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DRAWINGS ATTACHED

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(54) AUTOMATIC CHEMICAL ANALYSER

(71) We, XEROX CORPORATION of Rochester, New York, 14603, United States of America, a Body Corporate organised under the laws of the State of New York, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:

This invention relates to automatic chemical analysis and, more particularly, the invention relates to the automatic chemical analysis of body fluids, such as blood, urine, etc.

In the past, many routine, manual laboratory procedures have been conducted upon body fluids as an aid to the physician in determining, diagnosing, or preventing the various ailments which afflict mankind. As the science of medicine progresses and becomes more sophisticated in its analysis, new laboratory procedures and techniques are developed which analyze such fluids in search for a hidden clue which will establish or negate the existence of a particular affliction.

At the same time that medical science is developing new tests to aid in pinpointing particular afflictions, the population of the United States, and of the world, is expanding at an enormous rate. New phrases, such as "the population explosion", have been coined to express this physical phenomenon which is presently occurring and will continue to occur throughout the existence of mankind. Thus, with more tests being conducted per person and more people coming in need of such tests with each passing day, it becomes evident that more people must be trained and/or new devices must be developed to meet this onrushing demand.

This problem has plagued mankind for many years and it is equally evident that the solution of training more qualified people to conduct this ever increasing amount of clinical analysis has not been equal to the task. Most clinical departments are headed by a resident pathologist or a licensed medical technologist who supervises a trained staff of laboratory technicians. As the majority of laboratory technicians are young, unmarried girls the turn-over rate is unusually high because of ensuing marriages which require the wife to devote her time to the needs of her family. The resulting manpower shortage places a limit both upon the quantity of clinical tests which can be conducted as well as the quality for, when one is burdened with an ever increasing amount of work which must be completed within a unit period of time, human errors are bound to become more prevalent.

To fulfill this ever increasing demand which is not being adequately met by our expanding technical labor supply, new devices have been developed to assist the laboratory technician in conducting a greater number of tests per unit time. Many of these devices took the approach of merely mechanizing, or automating, the purely manual operations of the ordinary clinical chemist or analyst. Exemplary devices of this type are shown by Hewson U.S. No. 2,560,107; De Seguin Des Hons U.S. No. 3,143,393; Baruch in U.S. Nos. 3,193,358 and 3,193,359; and Natelson U.S. No. 3,219,416. This approach results in a device having test tubes, funnels, reagent containers, pumps and other associated means for bringing a particular sample and the necessary reagents together to perform a desired analysis. Though the devices unquestionably perform more analyses per unit time the devices, as a whole, are subject to other objections which are similar to those stressed when a technician manually performs the analytical procedures. That is, the repetitious use of the same laboratory equipment for a plurality of

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distinct analyses poses the problem of contamination. To overcome this detrimental aspect a significant portion of the operating time of the devices must be allocated to the repetitious cleaning of the equipment to provide a clean environment for subsequent tests. As a result, the efficiency in terms of the number of tests which can be conducted per unit time is drastically diminished.

An additional detrimental feature of such devices, as well as other prior art devices, is the fact that they are initially programmed to perform a plurality of tests of a single type. That is, a plurality of samples are taken and a single test, for example, blood sugar, is run on each sample. The device must be reprogrammed to provide for additional tests on the remaining portions of the samples. In many instances, the devices cannot be so reprogrammed or to do so requires substantial modification or repositioning of the component parts by the operator. These modifications reduce the flexibility of the device and further diminish the improvement which can be obtained in performing purely manual procedures through mechanical means.

A recent automatic apparatus which has achieved some measure of success is the "Auto-analyzer" produced by the Technicon Instruments Corporation of Chauncey, New York. This apparatus is disclosed in the patents to Skeggs U.S. Nos. 2,797,149 and 2,879,141, as well as numerous other United States patents assigned to the Technicon Instruments Corporation. As disclosed in the aforementioned patents, a fluid sample to be analyzed is passed through tubular passages and a proportioning pump comprising a plurality of resilient flexible tubes, a platen, and a plurality of pressure rollers. The sample to be analyzed with one or more processing fluids is passed through one side of a dialyzer while one or more secondary processing fluids are passed through the other side of the dialyzer thereby resulting in the separation from the sample of various constituents which pass through the dialyzer to the secondary processing fluids. Air is introduced into both flow streams before they reach the dialyzer to break up each stream into a plurality of liquid segments separated by air segments or bubbles. The air segments are stated to have the dual purpose of separating the sample from each other as well as providing a cleansing action between successive samples in order to prevent cross-contamination. The diffusate passing from the dialyzer is subjected to treatment to induce a colour change in the liquid segments thereof indicative of the concentration of the constituent for which the sample is being analyzed. Normally, the air or other inert fluid which has been introduced into the fluid streams to segment the fluid material is then withdrawn from the stream at a point before colorimetric examination leaving a continuous liquid stream for final examination. Finally, the treated diffusate is directed to a flow cell of a colorimeter in which it is subjected to colorimetric examination to provide a quantitative measurement of the constituent being analyzed.

Present commercial forms of the "Auto-analyzer" comprise a plural-channel apparatus which simultaneously performs a plurality of different tests on a single test sample. Though there are approximately twenty different tests which can be conducted with the apparatus, it is not possible to program the analyzer to perform any number of tests less than the number of channels. Thus, when a physician requires only one or two tests to be conducted upon a particular sample, the unit cost per test is increased because the apparatus is non-selective and must do a profile analysis. Additionally, since a plurality of different samples having different concentrations of the constituent for which the sample is being analyzed are being passed through the flexible tubular passages, the flow cuvette, the dialyzer, etc., there is a problem of sample carryover or contamination which can have a significant effect on the reliability of the analytical data. To reduce contamination, cleansing fluids are generally provided in an attempt to assure a contamination free environment. This further encumbers an already complicated apparatus.

In operation, the proportioning pump passes the various fluids through a maze of flexible tubes. The repetitious flexing and continuous working of the tubes causes them to wear out very readily with the result that minute cracks can be found throughout. This results in areas which are more easily wetted by sample material passing therethrough thus adding to the contamination factor of the overall apparatus, as well as increasing the operational expense occasioned by the necessity of replacing worn tubing. Preceding each period of operation there is a required lengthy warmup period. Additionally, a calibration curve must be obtained each time the machine is started up to assist in compensating for various deviations which may occur during non-operating periods and, for proper analysis, a second calibration curve must be obtained at the end of each run to pinpoint deviations which occur during operation. Finally, the preliminary analytical data obtained through use of this apparatus with respect to each particular sample must be correlated with the aforementioned calibration curves to provide the final analytical data in a form considered reliable by the physician. Such factors limit the total effect such an apparatus can have on clinical analysis as significant amounts of time must

be spent by the technician in calibrating the apparatus and subsequently placing the analytical data so obtained in a reliable form.

According to the invention there is provided an automated analytical apparatus comprising means to store a plurality of reagent-storing, disposable reaction containers; means to transfer at least a portion of a sample from a sample storage site to a reaction compartment in one of said reaction containers; at least one means enabling addition of at least one reagent stored within a storage compartment in the said one disposable container to the reaction compartment; means to monitor at least one of the physical properties of the reaction mixture within the reaction compartment and means to advance said containers past said sample and reagent addition enabling means to said monitoring means.

An example of the invention will now be described with reference to the accompanying drawings in which:

Figure 1 is an enlarged sectional perspective view of an exemplary disposable container which is to be used with the present invention;

Figure 2 is an enlarged sectional view of another exemplary disposable container which is to be used with the present invention;

Figure 3 is a top view of the disposable container of Figure 2;

Figure 4 is an enlarged sectional perspective view of still a further exemplary embodiment which is to be used with the present invention;

Figure 5 is an enlarged side view of still a further exemplary embodiment for use with the present invention;

Figure 6 is a top view of the exemplary container of Figure 5;

Figure 7 is an enlarged perspective view of an automatic analytical system as contemplated by the present invention;

Figure 8 is a perspective view of a further exemplary disposable container for use with the present invention;

Figure 9 is a perspective view of an automatic analytical system utilizing the data card-type disposable container of Figure 7; and

Figure 10 is a perspective view of still a further automatic analytical system as contemplated by the present invention wherein the disposable containers are carried by an elongated tape.

Referring to Figure 1, there is seen a container 10 having a lower section 11 and an upper storage section 12. Section 11 has an end portion 13 and side wall 14, the upper end of side wall 14 terminating in a flange 15 provided for the fixed engagement of section 11 with storage section 12. One or more chambers 16 are provided in section 12 for the storage of appropriate reagents 17. Chambers 16 are in communication with reaction compartment 18. Plugs 19 in slidable engagement with the walls of chambers 16 are provided to prevent the premature spilling of contents 17 into the reaction compartment. Additional plugs 20 are provided at the upper end of chambers 16 in a similar manner to prevent the loss of the reagent material from the disposable container. Rods 21 between each set of plugs in a particular chamber are provided to assist in forcing plugs 19 out of chambers 16. The application of a pushing force upon plugs 20 will be transmitted through rods 21 to plugs 19 thereby forcing the latter plugs and the contents of chambers 16 into reaction compartment 18. A channel 22 passing through storage section 12 and extending into compartment 18 is provided for the addition of sample; distilled water; and reagents which were not stored, for one reason or another, in the storage chambers. In the preferred embodiment, it is contemplated that all the necessary reagents will be stored in chambers 16. Side wall 23 of channel 22 extends into compartment 18 and terminates in flange 24 defining aperture 25. It is through channel 22 and aperture 25 that the additional materials are added to compartment 18. Channel 26 extends through section 12 into communication with compartment 18 to permit venting of gases trapped in the compartment during sample and reagent addition. The vent channel can be parallel to the main channel 22 (as shown in Figure 2), or it can have a short horizontal or slanted leg connecting two vertical legs thus defining a trap in the venting passage which will aid in preventing the premature spilling of the contents of compartment 18. As shown, the entire unit comprises cylindrical shaped elements offering little or no resistance, corners, etc., which would hinder the movement of such containers. However, there are flanges, etc., which can be grasped by transportation means to move the disposable container through the automatic analyzer system from its storage magazine to the disposal station. It should be understood, however, that any desired shape of either the container or its component parts may be chosen and that the cylindrical form has been herein described only because of its aforementioned advantages.

In operation, container 10 is taken from a supply magazine and passed to a sample addition station where the proper amount of sample diluted with distilled water is aliquoted into compartment 18 through channel 22 and aperture 25. The sample-containing container is then passed to a reagent addition station where the application of a pushing force on plugs 20 forces plugs 19 and re-

agents 17 out of chambers 16. Preferably, plugs 19 are made of a material which will either float on the surface of the liquid in compartment 18 or sink to the bottom thereof. This is desirable so that they will not interfere with any subsequent optical analysis (i.e., they will not be in the optical path). Container 10 is passed to a mixing station where it is maintained for a time sufficient to ensure the dissolution of all solid materials in the liquid contained in compartment 18. The container next passes to an incubation station where appropriate reaction conditions are imposed upon the materials within the container for a time sufficient to complete the desired reaction which is then measured at a detection station. It is not necessary that the mixing and incubation stations be separate and distinct as it is feasible to have one station where both results can be achieved. At the detection station, for example, a cylindrical light source probe can be passed down through channel 22 until it rests upon flange 24. Flange 24, a constant fixed distance from end wall 13, acts to define a fixed optical path through the reaction mixture. By carefully controlling the manufacture of disposable containers 10, the optical path is a constant for each and every analysis. Appropriate detection means, such as a photo-multiplier tube, placed below optically transparent end portion 13 of compartment 18 operates in combination with the light source to yield the desired test data. Alternatively, light can be passed through the optically transparent side wall 14 of the container to similar detection means. Additional means are associated with container 10 to identify the particular sample as to its source and as to the particular test being run thereon. For example, the container can have magnetic coding placed on the side thereof or a data punch tape attached thereto. The associated mechanisms for placement and read-out of such data are well known in the art. Means are also provided to correlate such information to establish an appropriate record for subsequent reference. The container finally passes to a disposal station where it is withdrawn from the system.

An alternate embodiment of the present invention is shown in Figures 2 and 3 wherein lower section 11 is partitioned by interior walls 30 and 31 into three distinct compartments 32, 33 and 34. Walls 30 and 31 formed as an integral part of lower section 11 terminate in lips 35 which are held snugly in grooves provided in upper section 12 thereby creating the three separate and non-communicating compartments. In compartment 32 there is a reference material, normally diluted reagent. Chamber 33 has provided therein a solution of the material being tested in the absence of reagents. In certain instances, one or more reagents can be added to this latter solution, provided the reagents do not carry the reaction to completion or do not adversely affect, in any other way, the optical analysis. Through use of these two solutions measurements are made which cancel the error due to variations in the reagent or sample material. Into chamber 34 there is introduced the sample material to be tested along with the appropriate diluents and one or more reagents. As in Figure 1, channel 22, reagent-storage chambers 16, and venting channel 26 are provided in upper section 12 for introducing sample and stored reagents into each chamber 32, 33, and 34, and for venting gases which would otherwise be trapped in the respective chambers.

In operation, the container of Figures 2 and 3 follows the same path as the container of Figure 1. At the detection station, however, light beams are passed through each chamber to obtain the desired analytical data. Light sources can be passed down into channels 22 in communication with each of the respective chambers as in Figure 1. Once again, there will be a fixed optical path leading to a detection unit, such as a photo-multiplier tube. Alternately, the beam of light can be passed through the side walls of each chamber. To eliminate adverse effects from light scattering, walls 30 and 31 can either be made of an opaque material or can be coated with an opaque material to prevent the passage of light therethrough.

To calibrate the detection mechanism, "standard" samples containing known amounts of the constituents under analysis are passed through the detection station. The detection mechanism will analyze each standard and then adjust itself for deviations from the known value. Alternatively, a standard solution can be used in place of the diluted reagent in the disposable container. This standard solution can be injected into the disposable container at any point in the system prior to optical analysis and will obviate the need for passing distinct standards through the system. Once again, the detection mechanism will analyze each standard and adjust for deviations from the known value. Use of this disposable container in combination with a continuous self-calibrating optical read-out station will yield analytical data of exceptional reliability.

Referring to Figure 4, there is seen a disposable container wherein either the vent channel or one of the reagent storage chambers is utilized as the sample addition channel. Specifically, container 10 has a lower section 11 which, in this instance, is the same as the lower section in Figure 1 and an upper section 12. One or more chambers 16 in communication with reaction compartment 18 are provided in section 12 for the storage

of appropriate reagents 17. Any gases which might be trapped in the reaction compartment during sample and/or reagent addition are vented through channel 26. Plugs 19 and 20 at each end of chambers 16 prevent the premature spilling of reagents 17 into the reaction compartment or out of the container, respectively. It should be noted that in this embodiment no rods are provided to connect the plugs at the opposite end of each chamber for it has been found that by selecting a proper length to diameter ratio it is possible to push plugs 20 the entire length of the chamber with relative ease. By selecting the proper ratio, the plug can be moved the entire distance without jamming or "freezing" so that all the contents of the chamber can be emptied into the reaction compartment to produce the desired reagent mixture.

The disposable container of Figure 4 differs additionally from the container of Figure 1 in that upper section 12 has a lower extension 36 of an outside diameter equal to the inside diameter of the lower section; accordingly, this results in a very snug, slidable engagement of the upper section and the reaction compartment. Upper section 12 has an end wall 37 which limits the downward movement of section 12 into lower section 11. In the bottom of the container there is a magnetic stirring bar 38, for example a small cylindrical section of stainless steel wire. Should the magnetic material have a deleterious effect on the assay, then the stirring bar is entirely covered with a material which will not interfere with the analytical procedure, such as glass or plastic. With the reaction mixture in the lower compartment, the disposable container is moved to a mixing station where an external rotating magnetic field is applied, such as by a rotating magnetic bar. The rotation of the magnetic bar within the disposable container creates a vortex with the liquid material in the reaction compartment being substantially higher along the outside wall of the chamber than it is in the center. By regulating the rotational speed of the magnetic stirring bar it is possible to thoroughly mix all the reagents with the sample as well as to clean the walls of the reaction compartment and the lower extension of the upper section of the undissolved reagents. This ensures that all reagents are present in the reaction mixture in the proper amounts.

Referring to Figures 5 and 6 there is seen a disposable container 50 having two separate lower compartments 51 and 52. Each lower compartment has a bottom wall 53, exterior side walls 54, 55, 56 and interior walls 57. As shown, walls 54 and 56 are vertically disposed while walls 55 and 57 diverge outwardly from end wall 53 toward the top of each respective compartment. Bottom walls 53 are in a shape of a rectangle with slightly rounded edges and corners (though the shape is not in any way critical). Since the walls 55 and 57 diverge slightly from end wall 53 toward the upper part of the compartments, the opening at the top of the compartment also defines a rectangle having the same width as the rectangle formed by bottom wall 53 but with a slightly longer length. The shape of the opening is not critical as long as it will not interfere with the introduction of sample and reagents into the lower compartment. The sloping walls 55 and 57 channel all materials downward toward the bottom of the unit. It is equally true that side walls 54 and 56 can be slanted inwardly from the opening down toward bottom walls 53 and thus aid in channelling material to the bottom of the compartment, however, it is preferred that they remain parallel for optical reasons. The wall portions of compartments 51 and 52 terminate in a horizontal flange 58 which encircles the outer perimeter of the two compartments and holds them together as a distinct unit. Flange 58 terminates in an upwardly extending lip 59 which is folded inwardly to hold reagent storage section 61 in place on top of horizontal flange 58. Interior walls 57 extend slightly above the plane of horizontal flange 58 and are connected to each other at a point 60 thus defining a distinct barrier between compartments 51 and 52.

Resting on flange 58 and barrier 60 is reagent storage section 61. Section 61 comprises an upper layer 62 defining a plurality of reagent storage chambers 63 in the form of "top-hats". On the underneath or open portion of layer 62 is a thin weak restraining layer (not shown) for holding the reagents in the respective chambers. Application of force on the top of the chambers will cause the shearing of restraining layer at a point immediately below the "top-hat" resulting in the inversion of "top-hat" 63. Reagent or other material stored therein will be emptied into the lower compartment. In each of the bottom compartments there is a magnetic stirring bar 75 substantially encased in a material which is non-deleterious to the analysis.

The disposable container of Figures 5 and 6 is used in conjunction with a double-beam detection mechanism. In one compartment there is provided a solution of the material being tested with all the reagents which will bring the reaction mixture to the desired point for analysis. The other compartment contains a solution of the material being tested in the absence of reagents. In certain instances, one or more reagents can be added to this latter solution, provided the reagents do not carry the reaction to completion or do not adversely affect, in any other way,

the optical analysis. This latter solution is called a "critically incomplete blank" and will enable the analytical system to correct for the effects of the sample and the reagents added. To maintain the detection mechanism in calibration standard solutions are passed through the detection mechanism at intervals so the latter can adjust for deviations which occur during operation.

Referring to Figure 7, there is seen an automatic analyzer as contemplated by the present invention. Disposable containers 150 are stored in magazine 152 which is partitioned into a plurality of compartments 153, 154, 155, 156, etc. As previously indicated, each container 150 is a prepackaged chemical testing unit. Only like units are stored in the same compartment with other containers. Transportation means in the form of a grooved wheel 160 is provided to move the containers from the magazine 152 to the sample addition station 161. Wheel 160 has a plurality of grooves 162 disposed about the periphery thereof. An end wall 163 is provided at the bottom of each groove to hold the containers within the grooves. When using the disposable container of Figures 5 and 6 appropriate ledges are provided to support the container by flange 58. Tangential to transportation means 160 are two incubation wheels 166 and 167. Incubation wheels 166 and 167 also have a plurality of grooves 168 and 169, respectively, disposed about their periphery. A retaining wall 177 is positioned about the outer periphery of each grooved wheel in parallel spaced relationship to prevent the containers from accidentally falling out of the grooves after being positioned therein. The retaining wall is shown about wheel 167 but, for sake of simplicity, has been omitted from around wheels 160 and 166. Containers 150 are loaded onto transportation means 160 by any suitable means in response to an electrical signal. Once properly positioned on wheel 160, the container passes to the sample addition station 161 where the appropriate amount of diluted sample is added to the unit. In accordance with an appropriate input signal, sample addition station 161 withdraws the proper amount of sample from the initial sample-containing vessel (not shown) and deposits the sample along with the appropriate amount of diluent through conduit 164 into the reaction compartment within the container. Probes 165 are also provided to force reagents out of their storage chambers or top-hats into the reaction compartment. Each incubation wheel can have a different diameter and be revolving at a different rotational speed to provide a variety of retention times between the time the disposable container is first placed on the wheel to such time as it passes through the detection station. For example, incubation wheel 166 can have a ten minute incubation while wheel 167 has an incubation time of thirty minutes. Thus, a container can take, in the system as shown, one of three routes. First, it can be routed from wheel 160 to wheel 167, spending 30 minutes on wheel 167, and then be transferred to wheel 166 where approximately 10 minutes more are spent in incubation. Secondly, the container can be transferred from wheel 160 to wheel 166 for a 10 minute incubation or, finally, it can be transferred from wheel 160 to wheel 167 for a 30 minute incubation. What path will be chosen will depend upon the necessary incubation periods for the assay, as well as the manner in which the system is programmed to handle a plurality of assays simultaneously. It is preferred that transportation means 160 be revolving sufficiently rapidly so that little time is spent by the disposable container on that wheel after sample and reagent addition but before transfer to the incubation wheel. Further wheels can be provided along the outer periphery of incubation wheels 166 and 167 so that the disposable container can be sequentially passed through them to lengthen the incubation period. The disposal container, having the diluted sample and reagents mixed in the reaction compartment, is maintained on transportation wheel 160 until the groove comes in communication with a corresponding groove in an adjacent incubation wheel. At that time, the container is transferred from the groove in the transportation wheel to the groove in the incubation wheel by air pressure, a transfer ram or any other suitable transfer mechanism. While the disposable container is in the incubation station it passes through detection station 170. A similar detection station (not shown) is provided adjacent wheel 167. Light from source 171 passes through channels 172 in wheel 166, the cuvette compartment in the disposable container, and finally falls upon the detection unit, such as a photoelectric cell, 173. The magnitude of the electrical signal through photocell 173 is proportional to the light transmittance of the reaction product in the cuvette. This ouput signal which is indicative of the amount of a particular constituent in the sample is fed to a control panel and storage device for its storage. Means are also provided to identify the particular sample as being from a particular patient as well as the test being run thereon. Such information is also taken from the disposable container at this time and stored with the analytical data in similar manner. As the incubation wheel 166 revolves, the disposable container comes to a position 174 where it is ejected from the wheel into disposal station 175. A disposable container transferred to wheel 167 follows a similar procedure. If necessary, a

disposable container can remain in a groove on this, or any other, wheel for more than one revolution. Thus, several readings can be taken at regular intervals while the container is on the wheel. In this manner, the rate of a chemical reaction can be determined and transformed into meaningful data. For example, after numerous readings, the data so obtained can be correlated and reduced to a curve which defines the rate at which a chemical reaction within the reaction compartment is proceeding. For certain reactions, this rate is proportional to the concentration of the known constituent. Additionally, with respect to wheel 167 there is shown a secondary reagent addition station 176 provided for the addition of those reagents which were not emptied into the disposable container by probes 165 at station 161. As many secondary stations can be provided as are necessary for the particular procedures programmed into the system and they may be positioned wherever reagents need to be added. By providing more than one reagent addition station, it is possible to sequentially add reagents at the appropriate time in a particular analytical procedure.

A further exemplary disposable container is seen in Figure 8 wherein a record data card 90 has on one surface thereof a reaction container 91 sectioned into a plurality of compartments 92, 93, and 94. Strong seals are provided along the outer periphery of the container to securely bond it to the underlying substrate. Such seals can be, for example, strong thermally bonded heat seals or strong adhesive seals. Under application of a moderate force, as will hereinafter be described, these bonds will not rupture with the result that the reaction container remains securely fastened to the record card. Separating compartment 92, 93, and 94 are "weak" seals 98 which under the application of heat, vacuum, flexing or pressure are opened thereby providing a single compartment having the powdered reagents loosely mixed in the bottom thereof. Such seals can be either heat seals or weak adhesive seals. Appropriate data 95 is stored on the remaining portion of the record card in a form well known to those skilled in the art and which will, in conjunction with the appropriate means in the automatic analyzer, cause the proper analysis to be conducted on the sample and to identify the sample and test results as being of a particular patient. Powdered reagents 96 and 97 are stored, respectively, in compartments 93 and 94. If necessary, it is possible to store additional reagents in lower compartment 92. The desired number of compartments is determined by the number of reagents required for a particular analysis and the compatibility of mixtures of reagents. A plurality of reagents can be stored in a single compartment provided they are compatible throughout a long shelf life.

In operation, one or more of the reagent-containing compartments is manipulated to open the compartments and cause them to be in communication with lower compartment 92. The powdered reagent stored therein is deposited into the lower compartment and the diluted sample solution is injected through a needle into the compartment. Mechanical members or fingers (not shown) can be provided to reinforce a particular weak seal so that upon application of force to the reaction container, that particular weak seal will not be broken. In this manner, selective compartments can be emptied of their contents sequentially thereby adding flexibility to procedures which can be utilized with this system. The unit is then passed through a mixing and incubation station where it is held for a time sufficient to culminate the desired chemical reaction and thereafter it is passed to an optical read-out station, wherein one or more of the physical properties of the reaction mixture is monitored.

A fully automated analytical system using the flexible container of Figure 8 is shown in Figure 9 wherein a prepackage storage magazine 102 is partitioned into a plurality of compartments 103, 104, 105, 106, etc. As previously indicated, each reaction container 100 stored on data card 101 is a prepackaged chemical testing unit. Only like units are stored in the same compartment with other reaction containers. Transportation means in the form of a traversing card handler 107, reciprocating on runners 108 and 109, is positioned adjacent the opening of the magazine 102 for selecting, in response to a given input signal from control panel 110, the appropriate data card 101 for conducting a desired analysis. Appropriate samples are placed in the sample magazine 118 with each sample having its own separate identification. As shown, disposable syringe 113 is carried by revolving syringe head 114 which moves in a counterclockwise direction. An unused syringe first passes to diluent reservoir 117 where the proper amount of diluent, normally distilled water, is drawn up into the syringe. Turning counterclockwise, the diluent carrying syringe passes to magazine 118 where a small amount of sample is drawn into the syringe proper from a sample vessel 119. Simultaneously, a machine-readable number on the sample vessel is read and transferred to control panel 110. Control panel 110 compares this number with other data which has previously been stored therein and commands the proper test to be conducted upon this sample. Traversing card handler 107 moves to a position adjacent the proper compartment in the prepackage storage magazine 102 and

picks up a data card 101 having the appropriate container 100 for conducting the desired analysis. The traversing card handler then moves to a position adjacent the opening 111 in sample addition station 112. The data card is moved into sample addition station 112 where disposable syringe 113, after revolving 180' on head 114 from station 118, is positioned above the reaction container on the card. Syringe 113 is lowered by gear means 120 until the needle penetrates reaction container 100 and the diluted sample has been deposited therein. The sample material is injected into the reaction container either prior to, during, or after the appropriate reagents have been emptied from their storage areas into the lower compartment. If desired, mechanical members or fingers can be provided in the sample addition station which can be programmed to sequentially empty the contents of the reagent storage compartments into the bottom portion of the reaction container. Optionally, this diluted sample can be injected into the reaction container and thereafter diluted with distilled water from a separate injection source (not shown). At this time, a blank reading may be made by a detection unit if desired, the detection unit being located adjacent the sample material injection syringe or the members for emptying the contents of the reagent storage compartments. Unused syringes are stored in a syringe storing area 115 and are dropped by syringe dispenser 116 into open spaces in revolving syringe head 114 vacated by the disposal of used syringes. It is preferred that a disposable syringe be used for each sample material, thus, if a plurality of tests are to be conducted on a particular sample it will only be necessary to dispose of the syringe after the completion of the transfer of the plurality of aliquots. However, if the syringe is properly cleaned and steps are taken to prevent cross-contamination, each syringe can be used for as long as desired. Card 101 is then ejected from sample addition station 112 onto a second traversing card handler 121 reciprocating on runners 122 and 123. The traversing card handler deposits the card in the far-end entrance of incubation station 125. Prerecorded data on the data card determine when the card should leave the incubator and, consequently, the reaction container is held within the incubation station for a period of time sufficient to culminate the chemical reaction. At that point in time, the card is ejected from incubation station 125 and picked up by traversing card handler 121. For added flexibility, an additional traversing card handler (not shown) can be provided solely for the withdrawal of the data cards from the incubation station and the introduction thereof into the detection unit. If further reagents need to be added following the first incubation cycle, the data card is taken by traversing card handler to a reagent-addition station (which can be station 112 or a separate station) to receive additional reagents. The data card can then be placed back in incubation station 125 or sent directly to the detection station. From the traversing card handler 121 the data card is passed into slot 126 defining the detection station wherein one or more physical characteristics of the reaction mixture is monitored to obtain the desired analytical data. Within the detection station the analytical data obtained is immediately transferred to the data card to provide a complete record for future reference. After detection, the card is ejected from the detection station 126 at opening 127 and picked up by a traversing card handler. Once again, for added flexibility, a traversing card handler for solely picking up ejected cards from the detection zone can be provided. The data card is then taken to disposal station 128 where a card slicer 129 removes the portion of the card supporting the reaction container. The reaction container supporting portion of the card falls into a disposal cavity 130 while the data containing portion of the card is dropped into storage container 131. As shown, storage container 131 is not integrated with control unit 110 but it can be easily positioned to be an element thereof. If so positioned, the cards can be automatically read and data stored in an appropriate memory device for subsequent reference. In the device as described, the cards are taken by a technician and transferred to the control unit where the information contained on the data card is stored until such time as required by the physician.

After the first card for a given analysis has been deposited in the sample addition station 112, the traversing card handler 107 will immediately move to the proper compartment adjacent the magazine to receive a second card, and the entire process will be repeated for that particular analysis. It should be appreciated that there will be many cards at various locations within the system simultaneously. By simultaneously, it is not meant that the beginning and end of each analysis coincides with the beginning and end of other analyzes but rather that there is a substantial overlapping of the operational steps involved. Thus, one card will be in the sample addition station while another will be in the detection station Obviously, the analysis of the sample in the card in the detection station will be completed long before the completion of the sample now being deposited. However, since there is an overlapping of operational steps, such tests are considered to be simultaneous within the meaning of the word as used in this application.

Referring to Figure 10, there is seen an alternate embodiment of the present invention wherein the supporting substrate for the disposable container comprises an elongated tape 140 having a plurality of containers 141 stored thereon. The container-supporting tape is wound upon a storage reel 142 and threaded through a sample addition station 143, a mixing and incubation station 144, an optical read-out station 145 and thereafter finally deposited in a disposal station (not shown) or wound upon a take-up reel (also not shown). Tape 140 has appropriate sprockets therein, much like movie film, so it can be indexed from position to position. The supporting tape can have a magnetic coding or other means of printing in binary language. Sensors can read the recorded data and command various portions of the system to perform desired operations on the disposable container. Data, such as patient identification numbers and analytical results can be recorded thereon for storage and subsequent read-out. Ratchet and pawl mechanisms 146 are provided to move diluted sample injector 147 and detection means into and out of position. As is apparent this device does not have the flexibility of more fully automated systems, such as the one shown in Figure 7. Each particular sample must wait its turn for analysis and only one type of test or a fixed series of tests is normally programmed into a single reel (including the overall apparatus). However, for more flexible multiple testing a bank of reels is provided with each reel having a different testing prepackage so that a plurality of different tests are performed simultaneously (1) on aliquoted portions of the same sample or (2) on different injected samples. In this case the reels are mounted adjacent each other and the sample injector traverses back and forth across the reels.

Since it is expected that the disposable containers will be stored for long periods of time with the prepackaged reagents therein, the materials which make up the disposable container are selected so as not to contaminate or assist in the degeneration of the prepackaged chemicals. It is preferred that the construction materials be chemically inert or, at least, chemically inert to the reagents and any other chemicals which might, in a clinical environment, come in contact with the container. Once the reagents are prepackaged, the outer layer of the storage compartment will act as a barrier material preventing passage of contaminating factors. Alternatively, a plurality of disposable containers which do not have especially good long term barrier properties can be packaged together within a barrier material which will preserve the initial properties of the packaged reagents. Suitable materials include the fluorocarbons, such as trifluoromonochloroethylene, polytetrafluoroethylene, and Fluorothene (a product of Union Carbide Corporation); polyolefins, such as polyethylene, Ionomer (a cross-linked polyethylene based polymer produced by DuPont Corporation), and polypropylene; polystyrenes; polyvinyl chloride; polyethylene terephthalate; and polycarbonates. During use, the reaction mixture will be in the cuvette compartment for a relatively short period of time in comparison to the overall storage life of the prepackage unit; therefore, it is not necessary to provide the same stringent requirements for the material comprising the cuvette compartment as those set forth for the reagent storage section. The cuvette material is preferably inert to the reaction mixture under the ambient conditions which exist during the analysis. The material should also be non-porous thereby preventing the seepage of portions of the reaction mixture from the compartment. Optically, the materials should transmit a substantial portion of the light incident thereupon. It is preferred that the material be clear though a material with uniform haze may also be employed. Suitable materials include polypropylene, polyvinylchloride, polystyrene, polycarbonates, cellulose acetate, cellulose propionate, and cellulose butyrate. It is not always possible to provide a material having all the properties necessary for storage as well as having good optical properties for the cuvette. Accordingly, the reagents can be stored in a section constructed of one material and the cuvette is made out of a different material. The two sections are then united, in any suitable manner, to provide the prepackaged unit. It should also be noted that two or more layers can be laminated together to provide a storage chamber having the desired barrier qualities.

The disposable containers of Figures 1-4 have been made with tetrafluoroethylene and polypropylene upper sections for storing the reagents therein and polyethylene, polypropylene, polyvinyl chloride, polystyrene and cellulose propionate cuvettes. Each of these latter materials is sufficiently inert so as not to be affected by the reaction mixture during the incubation period. Each material transmits a sufficient portion of the light incident thereupon for analytical purposes. Polypropylene, however, is the least clear of the materials transmitting only about 80% and having a uniform haze. As previously indicated, since the haze is uniform and a substantial proportion of the incident light is transmitted this material can be used although it is not the preferred material from an optical viewpoint. Polyolefins, such as polyethylene or polypropylene, are suitable materials for use as the plugs within each of the reagent-storing recesses. An exemplary description of the materials

utilized in a preparation of a disposable container as described in Figures 5 and 6 include polyolefins for the reagent-storing section and the restraining layer holding the reagents in the top-hat chambers, and cellulose propionate as the cuvette. The restraining layer, as noted above, can be made from the same material used in producing the reagent storage section. To achieve proper shearing the layer should be approximately an order of magnitude thinner than the storage layer.

The manner of producing the disposable containers of the present invention is not considered part of this invention. In general, however, any suitable method can be used which will produce a container having the desirable characteristics. For example, injection molding can be used to obtain a rigid cuvette having good optical properties. In conjuction with this injection molded cuvette, an injection molded polyproylene top can be used for the storage of the necessary reagents. Thermoforming operations, such as pressure forming or vacuum forming, can also be used to produce portions of the disposable container which have intricate designs. Pressure forming, however, is preferred because it is possible by using high pressure air to get the plastic material into areas where it cannot be drawn by a vacuum.

The reagents stored within the chambers in the disposable container can be either in solid or liquid form. Liquid storage is not as desirable, however, because there is a greater propensity towards chemical reaction, either with the storage wall or with material permeating therethrough. Additionally, liquid materials are generally known to be more sensitive to light and other portions of the electromagnetic spectrum and, therefore, degrade faster unless adequate filters are provided to eliminate deleterious radiation. Accordingly, it is preferred to store the reagents in solid form whenever possible. When stored in the solid state, the reagents can be in powdered or tableted form, either singly or in combination with other compatible reagents. A disadvantage of storing two or more powdered reagents together is the extreme amount of surface area available for chemical reaction. Even though the materials are relatively non-reactive, prolonged storage under such conditions may have a deleterious effect on the reagent mixture. In such cases it would be best to package the materials separately or to package them in tablet form. Tableting sufficiently reduces the contact surface area between reagents as only point contact, in essence, is achieved when one spheroidal (or substantially spheroidal) tablet is placed on top of another. The actual form of the tablet is not critical but selection of a proper shape (for example to give minimum contact) may prove advantageous in increasing the storage life of the prepackaged reagents. Additionally, by providing detents in the storage chamber and snapping the tablets into place a plurality of tablets can be placed in the same chamber but spaced from each other to eliminate contact for possible chemical reaction. In this approach, if sufficiently strong detents are provided the restraining layer of Figures 5 and 6 or the plugs of Figures 1-4 can be omitted in analytical procedures wherein all reagent tablets are dropped into the reaction compartment before mixing or it is not disadvantageous to have the reaction mixture splash upon a tablet which has not been dropped into the mixture. Tableting provides a feasible method for accurately depositing the proper amount of chemical reagent within a particular chamber. Severe dust and contamination problems may exist when a plurality of different powdered chemicals are being deposited into storage chambers which are a fraction of an inch apart. When a tableting form of reagent addition is utilized these problems are, at least, eliminated from the packaging line and placed in their own environment where they can be dealt with separately. It is, of course, necessary to use only those materials in the tableting process which will not have a deleterious affect on the analytical procedure. In any case, the reagents, whether stored in liquid or dry form, must be put into the reagent chambers in a measured amount, the tolerance of which is determined by the given analytical procedure. Finally, storage of the reagents, whether they are in powdered, tableted or liquid form, may be in a dry inert gas atmosphere, such as nitrogen. By providing an inert atmosphere, the relative chemical activity of the reagents are significantly reduced thereby increasing the shelf life of the prepackaged unit.

Many alternate container designs can be conceived which will achieve the advantageous results herein disclosed. While one embodiment has been shown for securing the upper section of Figure 5 to the lower section, many other ways of achieving this result can be utilized. For example, the upper section can be heat sealed to the lower section or the sections can be crimped together to provide a unitary structure. Further, many kinds of detection techniques can be used in conjunction with the disposable containers of the present invention. For example, after the sample and appropriate chemicals have been added to the reaction container, in the manner previously described, a probe can be lowered into the reaction mixture and a fraction of this solution aspirated in the flame of a flame

photometer. Detection proceeds using well known flame photometric technology. Besides flame photometry, other analytical techniques can be utilized. Thus, instead of passing a beam of light through the reaction mixture to a detection means positioned on the opposite side of the reaction mixture, an immersion probe, such as the one shown by Baruch in U.S. 3,263,553, can be passed in each reaction mixture to analyze for varying amounts of the known constituent.

Reference is made to co-pending application 32300/70 (Serial No. 1218750) divided from this application, and 56986/67 (Serial No. 1218748) which relate to identical and similar apparatus.

WHAT WE CLAIM IS:—

1. A automated analytical apparatus comprising means to store a plurality of reagent-storing, disposable reaction containers; means to transfer at least a portion of a sample from a sample storage site to a reaction compartment in one of said reaction containers; at least one means enabling addition of at least one reagent stored within a storage compartment in the said one disposable container to the reaction compartment; means to monitor at least one of the physical properties of the reaction mixture within the reaction compartment and means to advance said containers past said sample and reagent addition enabling means to said monitoring means.

2. Apparatus as claimed in claim 1 wherein said means to store a plurality of reaction containers comprises a magazine, said magazine being partitioned into a plurality of container storage compartments.

3. Apparatus as claimed in claim 1 or claim 2 wherein said storage and reaction compartments are separated from each other by weakly bonded walls so that said compartments can be brought into communication upon destruction of the weak bonds, wherein said means which enable addition of the reagent includes means to break the weak bonds separating the storage compartments from the reaction compartment.

4. Apparatus according to claim 3 further including means to reinforce a particular weak bond while another weak bond is being broken by said breaking means.

5. Apparatus as claimed in claim 1 or claim 2 wherein the containers are each carried by a record member and said storage and reaction compartments separated from each other by walls weakly bonded to the record member so that said compartments can be brought into communication upon destruction of the weak bonds, further including means to record data on at least one portion of the record member.

6. Apparatus according to claim 5 further including means for shearing the container from the portion of the record member having data thereon, and means to receive the data containing portion of the record member.

7. Apparatus as claimed in claim 1 or claim 2 wherein the containers are each carried by a record member and said storage and reaction compartments separated from each other by walls weakly bonded to the record member so that said compartments can be brought into communication upon destruction of the weak bonds, further including means to automatically store the data obtained by said monitoring means on at least one portion of the record.

8. Apparatus as claimed in any one of claims 1 to 7 further including means to incubate the reaction mixture within the reaction compartment of one of the disposable containers.

9. Apparatus as claimed in claim 8 comprising a sample magazine for the storage of a plurality of said containers, means to read instructions on the containers and to eject the appropriate container from said storage compartment in said magazine, means to receive the container from said storage compartment and transport the container to said sample addition station and said reagent addition station, means to eject the container from said sample addition station and said reagent addition station, means to receive the ejected container from said sample addition means and said reagent addition enabling means and transport the container to said incubation means, means to eject the container from said incubation means, means to receive the ejected container from said incubation means and transport the container to said monitoring means, and means to eject the container from said monitoring means after analysis.

10. Apparatus according to claim 9 wherein said means to receive the container from said sample addition means and said reagent addition enabling means and the means to receive the container from said incubation means are the same means.

11. Apparatus according to claim 9 or claim 10 wherein each receiver and transport means comprises a container carrier reciprocable along a straight line path.

12. Apparatus according to any one of claims 1 to 4 wherein said container advancing means comprises a wheel having a plurality of container-receiving grooves disposed about the periphery thereof.

13. Apparatus according to claim 12 wherein there are a plurality of container-receiving grooved wheels, said grooved wheels being in tangential relationship, and further including means to transfer a disposable container from a groove in one wheel to a groove in a wheel tangential thereto.

14. Apparatus according to claim 13

further including means to synchronously move said plurality of grooved wheels.

15. Apparatus according to any one of claims 12 to 14 further including a retaining wall disposed about the periphery of the or each grooved wheel to prevent the disposable containers from falling out of said grooves.

16. Apparatus according to any one of claims 1 to 15 wherein said reagent addition enabling means includes at least one probe and probe drive to force out the contents of a reagent storage chamber in the disposable container.

17. Apparatus according to claim 8 wherein said incubation means surrounds at least a portion of said advancing means.

18. Apparatus according to any one of claims 1 to 17 further including at least one separate means for enabling the addition of at least one reagent stored within the disposable container to the reaction compartment.

19. Apparatus as claimed in any one of claims 1 to 17 further including means for enabling the addition of a plurality of reagents stored within the disposable container to the reaction compartment.

20. Apparatus as claimed in any of claims 1 to 19 wherein said means to transfer sample portions includes means to dilute the sample portion added.

21. Apparatus as claimed in any of claims 1 to 19 wherein said sample transfer means includes means to inject the sample into the reaction compartment of the disposable container.

22. Apparatus as claimed in claim 21 wherein said sample injection means includes a revolving syringe head, a syringe holder supported by said syringe head, and indexing means to move said injection means into and out of the reaction compartment.

23. Apparatus as claimed in claim 18 wherein the separate reagent addition enabling means is located further along the path of travel of said containers from the first-mentioned reagent addition means.

24. Apparatus according to claims 1 to 23 wherein said monitoring means includes a light source and a light detection means, said detection means being positioned on the opposite side of the reaction mixture from said light source, said detection means being responsive to the variations in light transmitted through the reaction mixture.

25. Apparatus according to claims 1 to 24 wherein there are a plurality of said monitoring means.

26. Apparatus as claimed in claim 25 wherein said additional monitoring means is located adjacent said sample transfer means for monitoring the reaction mixture adjacent the sample transfer means.

27. Apparatus as claimed in claim 25 wherein said additional monitoring means is located adjacent said reagent addition enabling means for monitoring the reaction mixture adjacent the reagent addition enabling means.

28. Apparatus as claimed in claim 8 or any claim dependent thereon further including means to recycle an analyzed disposable container from said monitoring means back to said incubation means for further incubation prior to additional analysis.

29. Automated analytical apparatus as claimed in claim 1 substantially as herein described with reference to and as illustrated in the accompanying drawings.

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FIG.1.

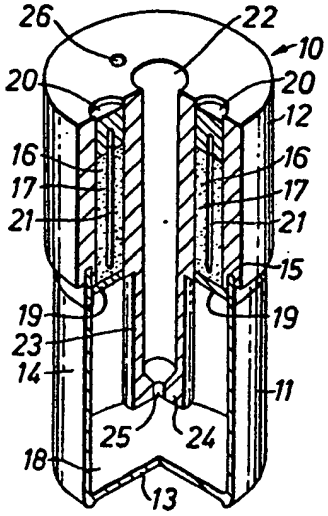

FIG.2.

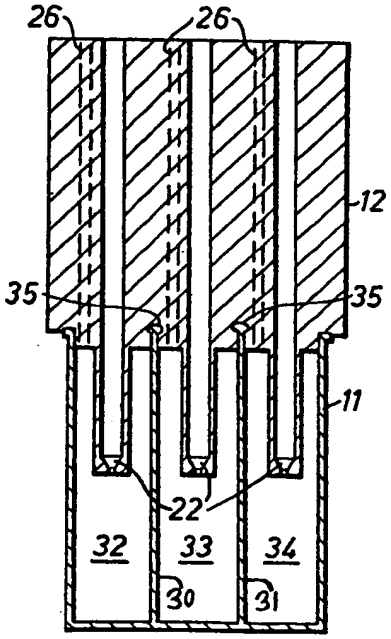

FIG.4.

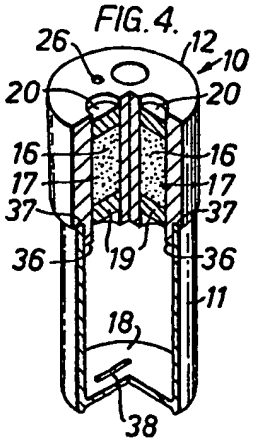

FIG.3.

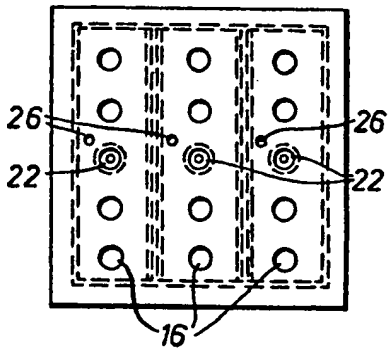

FIG.5.

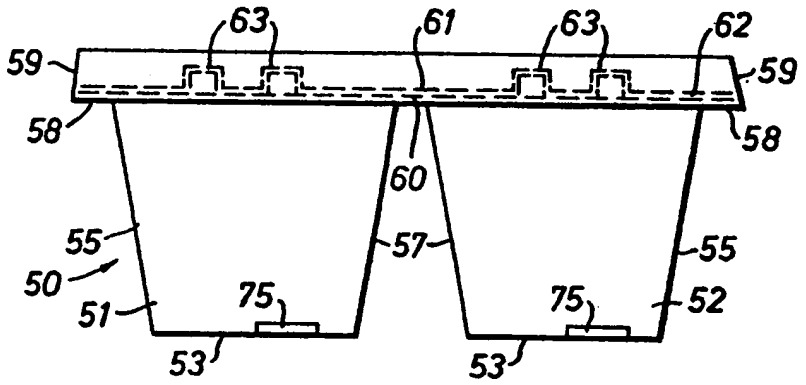
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FIG.6.

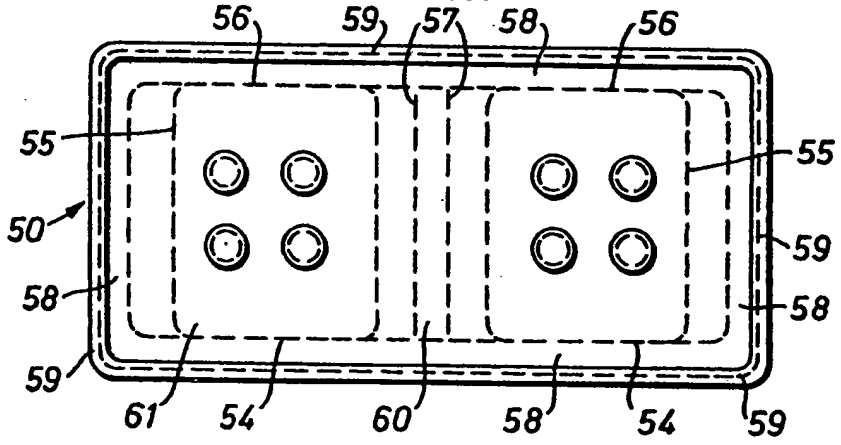
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FIG. 7.

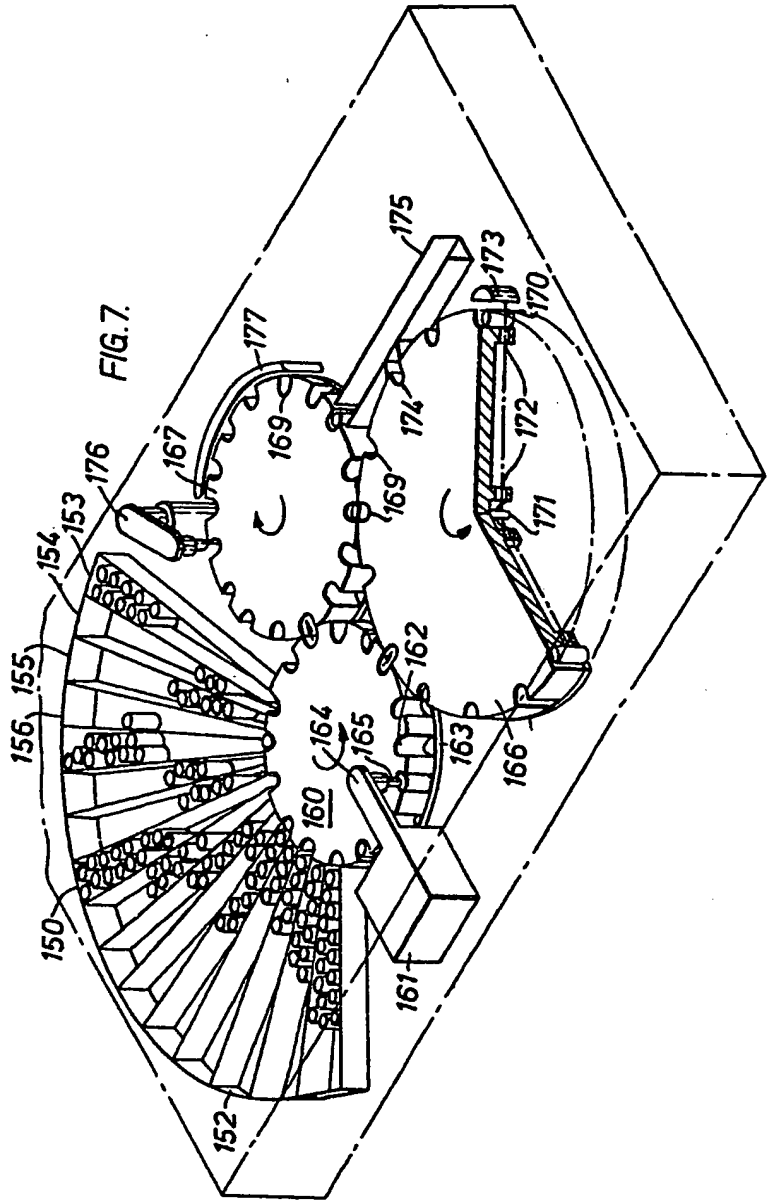

FIG.8.

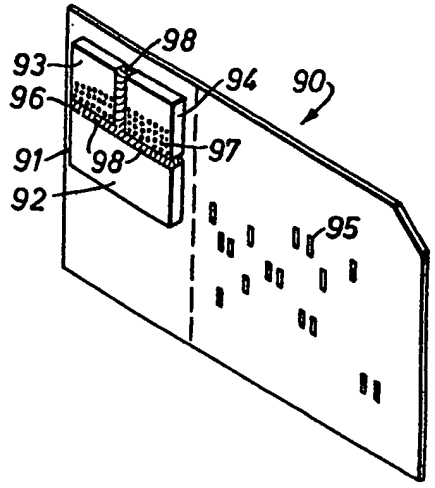
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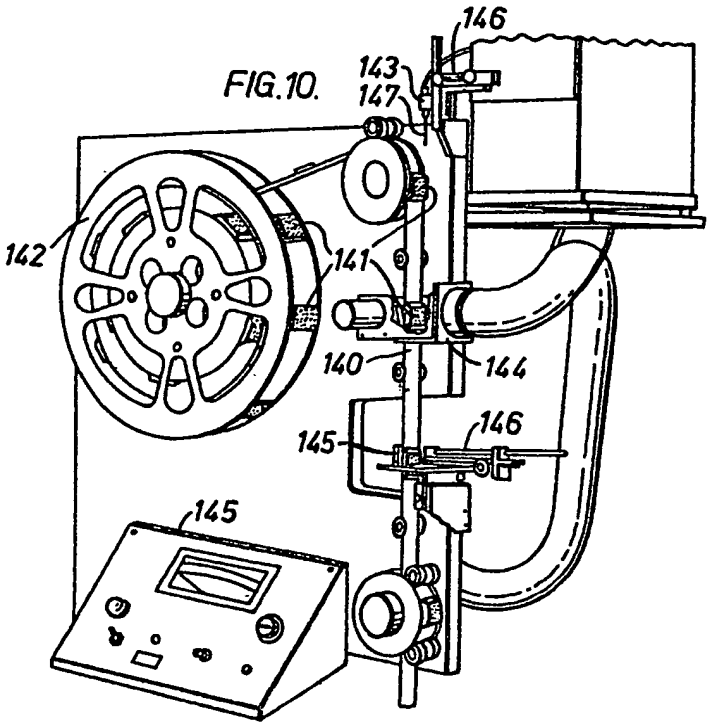
FIG.10.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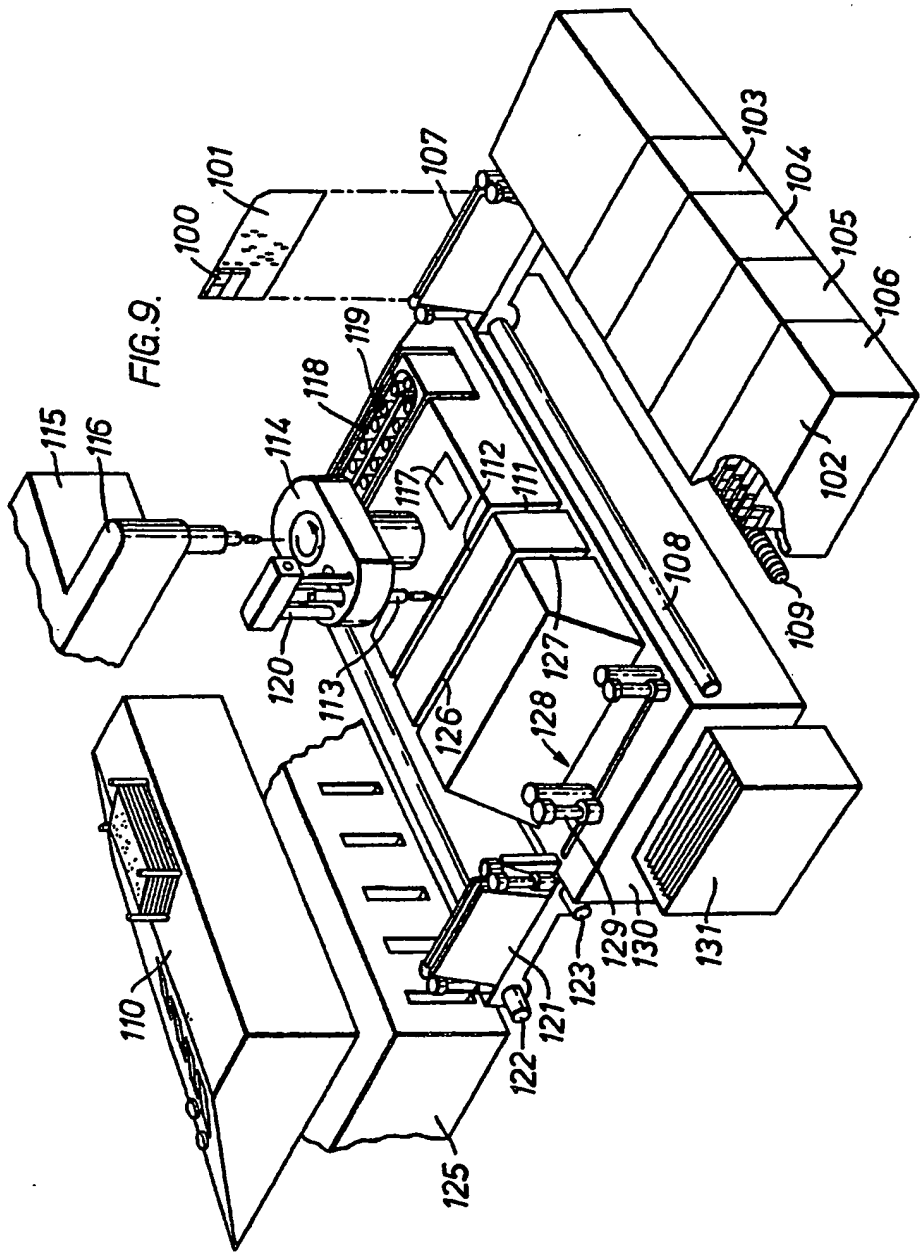

FIG. 9.